Exhibit 12

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. 02N–0417]

RIN 0910–AC48

Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its patent submission and listing requirements for new drug applications (NDAs). The final rule clarifies the types of patents that must and must not be submitted and revises the declaration that NDA applicants must provide regarding their patents to help ensure that NDA applicants submit only appropriate patents. The final rule also revises the regulations regarding the effective date of approval for certain abbreviated new drug applications (ANDAs) and certain other new drug applications, known as 505(b)(2) applications, submitted under the Federal Food, Drug, and Cosmetic Act (the act). In certain situations, Federal law bars FDA from making the approval of certain ANDA and 505(b)(2) applications effective for 30 months if the applicant has certified that the patent claiming a drug is invalid or will not be infringed, and the patent owner or NDA holder then brings suit for patent infringement. The final rule also states that there is only one opportunity for a 30-month stay in the approval date of each ANDA and 505(b)(2) application. The final rule will make the patent submission and listing process more efficient as well as enhance the ANDA and 505(b)(2) application approval processes.

DATES: *Effective Date*: This final rule is effective on August 18, 2003.

Compliance Date: The compliance date is December 18, 2003, for the submission of information on polymorph patents.

FOR FURTHER INFORMATION CONTACT: Jarilyn Dupont, Office of Policy and Planning (HF–11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–3360.

SUPPLEMENTARY INFORMATION:

I. Introduction

This final rule revises implementing regulations in part 314 (21 CFR part 314) for certain statutory amendments to the act, 21 U.S.C. 301 *et seq.*, relating to new drug applications and generic drug approvals. The statutory provisions were added to the act through the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417 (21 U.S.C. 355, 360cc; 35 U.S.C. 156, 271, 282) (''Hatch-Waxman Amendments'')). These statutory provisions reflect an attempt to balance two competing interests: Promoting competition between ''brand-name'' or ''innovator drugs'' and ''generic'' drugs, and encouraging research and innovation. The act promotes competition by creating a process to expedite the filing and approval of ANDA and 505(b)(2) drug applications (applications submitted under the provisions of section 505(b)(2) of the act) and for resolving challenges to patents in court before marketing begins. At the same time, the act encourages research and innovation by protecting the patent interests of the patent owner and innovator drug company.

The final rule maintains a balance between the innovator companies' intellectual property rights and the desire to get generic drugs on the market in a timely fashion. The final rule limits to one per ANDA or 505(b)(2) application the maximum number of statutory 30-month stays of approval to which an innovator will be entitled when it submits multiple patents for the same NDA. Eliminating multiple 30-month stays will speed up the approval and market entry of generic drugs. The final rule also clarifies patent submission and listing requirements, which will reduce confusion and help curb attempts to take advantage of this process. Specifically, patents claiming packaging, intermediates, or metabolites must not be submitted for listing. Patents claiming a different polymorphic form of the active ingredient described in the NDA must be submitted if the NDA holder has test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.

A. What Are the Statutory Provisions Which Affect Patent Submissions and the Approval of New Drugs?

To explain why we (FDA) issued the proposal, we first describe how Federal law requires NDA applicants to file patent information and how that patent information can affect the approval of ANDA and 505(b)(2) applications. (We will refer to these as ''ANDA and 505(b)(2) applicants'' or ''ANDA or 505(b)(2) applicants'' and refer to their applications as ''ANDA and 505(b)(2) applications'' or ''ANDA or 505(b)(2) applications'' throughout the remainder of the preamble of this document.)

Section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) requires all NDA applicants to file, as part of the NDA, ''the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.'' Section 505(c)(2) of the act (21 U.S.C. 355(c)(2)) imposes a similar patent submission obligation on holders of approved NDAs when the NDA holder could not have submitted the patent information with its application.

Under section 505(b)(1) of the act, we publish patent information after approval of an NDA application in our approved drug products list entitled ''Approved Drug Products With Therapeutic Equivalence Evaluations.'' This list is known popularly as the ''Orange Book'' because of its orange-colored cover. If patent information is submitted after NDA approval, section 505(c)(2) of the act directs us to publish the information upon its submission.

The act also requires ANDA or 505(b)(2) applicants to make certifications regarding each of the listed patents pertaining to the drug they intend to reference (see sections 505(b)(2)(A)(i) through (b)(2)(A)(iv) and 505(j)(2)(A)(vii)(I) through (j)(2)(A)(vii)(IV) of the act (21 U.S.C. 355(b)(2)(A)(i) through (b)(2)(A)(iv) and 21 U.S.C. 355(j)(2)(A)(vii)(I) through (j)(2)(A)(vii)(IV)). In brief, these certifications state that:

- Patent information has not been filed,
- The patent has expired,
- The patent will expire on a specific date, or
- The patent is invalid or will not be infringed.

If the ANDA or 505(b)(2) applicant certifies that the patent is invalid or will not be infringed (a certification known as a ''paragraph IV'' certification because it is the fourth type of patent certification described in the act[1]), the act requires the applicant to notify the

[1] Paragraph IV throughout also refers to paragraph iv, the comparable provision in section 505(b)(2)(A) of the act.

NDA holder and patent owner (see sections 505(b)(3) and 505(j)(2)(B) of the act (21 U.S.C. 355(b)(3) and 355(j)(2)(B)). The notice states that an ANDA or 505(b)(2) application containing a paragraph IV certification to a listed patent has been submitted for the NDA holder's approved drug product (known as the ''listed drug''). The notice also includes a ''detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed'' (*id.*). If the NDA holder or patent owner brings an action for patent infringement within 45 days after notice of the paragraph IV certification has been received, then we may not make the approval of an ANDA or 505(b)(2) application effective for 30 months, or such shorter or longer period as a court may order, or until the date of a court decision (see sections 505(c)(3)(C) and 505(j)(5)(B)(iii) of the act (21 U.S.C. 355(c)(3)(C) and 355(j)(5)(B)(iii)). (We will refer to the date the approval of an ANDA or 505(b)(2) application is made effective as the ''approval date'' throughout the remainder of this preamble.)

B. What Did the Proposed Rule Say?

In the **Federal Register** of October 24, 2002 (67 FR 65448), we published a proposed rule (proposed rule) that would address:

- The types of patents that must and must not be submitted by NDA applicants and NDA holders or patent owners (for purposes of this preamble, an NDA applicant is someone who is seeking FDA approval of a specific new drug application or supplement, whereas an NDA holder is someone whose NDA we have approved);
- The types of patents that we will list in the Orange Book;
- The patent declaration that NDA applicants must submit as part of an NDA, an amendment, a supplement, or when submitting information on a newly issued patent; and
- The 30-month stay of the effective date of approval for an ANDA or 505(b)(2) application.

The preamble to the proposed rule noted that, on occasion, we have seen NDA holders submit new patents for listing shortly before other listed patents for the same drug were to expire (see 67 FR 65448 at 65449). We explained that, in some disputes over recently listed patents, the parties had questioned whether particular patents met the regulatory requirements for submission and listing in the Orange Book. These disputes sometimes resulted in judicial decisions that are inconsistent with our regulatory policies or our interpretation of our own regulations (*id.*). We proposed to clarify our regulatory policies regarding patent submission, listing, certification, and notice. We also issued the proposal to respond, in part, to concerns raised by the Bureau of Competition and the Policy Planning Staff of the Federal Trade Commission (FTC). On May 16, 2001, the FTC submitted a citizen petition to FDA (FDA docket number 01P–0248) (''FTC Citizen Petition'') asking for guidance concerning the criteria that a patent must meet before it is listed in the Orange Book. The FTC Citizen Petition asked us to clarify several patent listing issues and indicated that the FTC was conducting an extensive study of generic drug competition.

In July 2002, the FTC published the results of the study in a report entitled ''Generic Drug Entry Prior to Patent Expiration: An FTC Study'' (''FTC Report''). The FTC Report focused on the procedures used to facilitate a generic drug's entry into the market before the expiration of a patent or patents that claim the brand-name drug product. The FTC also recommended changing Federal law to ''permit only one automatic 30-month stay per drug product per ANDA to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant's ANDA'' (see FTC Report at page ii). The FTC Report explained ''To permit only one 30-month stay per drug product per ANDA should eliminate most of the potential for improper Orange Book listings to generate unwarranted 30-month stays'' (*id.* at page v (footnote omitted)). In an appendix to its report, the FTC asked us to issue a regulation or guidance clarifying whether an NDA holder could submit various types of patents for listing in the Orange Book. The types of patents for which the FTC sought clarification were patents that claimed metabolites, polymorphs, intermediates, product-by-process patents, and double patents (see FTC Report at pages A–39–A–45).

C. What Does This Final Rule Do?

The comments received expressed both support for, and opposition to, various provisions of the proposed rule. After careful review of these comments, we are making final most of the provisions of the proposed rule with certain modifications. The final rule:

- Allows a full opportunity for only one 30-month stay per ANDA or 505(b)(2) application;
- Prohibits the submission of patents claiming packaging, intermediates, or metabolites;
- Requires the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA;
- Adds a requirement that for submission of polymorph patents the NDA holder must have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA;
- Makes changes to the patent information required to be submitted and provides declaration forms for submitting that information to FDA, both with the NDA and after NDA approval; and
- Does not require claim-by-claim listing on the declaration form except for method-of-use patents claiming approved methods of use.

II. Comments on the Proposed Rule

We received over 35 comments on the proposed rule. The comments represented a diverse range of interests such as: Health insurance programs, brand name pharmaceutical companies, generic pharmaceutical companies, law firms, consumer organizations, pharmacy associations, the FTC, the New York Department of Health, large corporations, and individuals. In general, most comments supported the rule, either in whole or in part, and believed that the rule would help reduce prescription drug costs by making generic drugs available more quickly. However, other comments opposed the rule because they felt we had misinterpreted the act or because they felt that new legislation, rather than a regulation, was necessary. We describe the comments, and our responses to the comments, in this section. To make it easier to identify the comments and our responses, the word ''Comment'' in parentheses, will appear before the description of the comment, and the word ''Response'' in parentheses, will appear before our response. We also have numbered each comment to make it easier to identify a particular comment. The number assigned to each comment is only for organizational purposes. It does not signify the comment's value, importance, or the order in which we received it.

A. Comments on Specific Aspects of the Proposed Rule

1. What Patents Must and Must Not Be Submitted? (Section 314.53(b))

Proposed § 314.53(b) would require NDA applicants and holders or patent owners to submit information on the following types of patents for listing in the Orange Book. In brief, the proposed

rule would clarify that we would list only patents that claim:

- The drug substance (ingredient);
- The drug product (formulation and composition); and
- Method of use.

Proposed § 314.53(b) would not allow listing of process patents and patents claiming packaging, metabolites, or intermediates.

a. *Patents Claiming a Drug Substance—Must Patents that Claim the ''Same'' Active Ingredient Be Submitted and Listed*? For patents that claim a drug substance, the proposal stated that an applicant ''shall submit information only on those patents that claim the form of the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application.'' We explained that an NDA applicant or holder would determine whether the drug substance was the ''same'' as the active ingredient in the NDA by considering ''whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability'' (see 67 FR 65448 at 65452).

Drug substances that are the same active ingredient, but that are in different physical forms, are often called ''polymorphs.'' For example, the different crystalline forms of a drug substance are sometimes known collectively as polymorphs, and drug substances with different waters of hydration are sometimes referred to as ''polymorphs'' as well. (For purposes of this final rule, polymorphs include chemicals with different crystalline structures, different waters of hydration, solvates, and amorphous forms.) Under the proposed rule, an NDA applicant or holder would be required to submit a patent claiming a different polymorph from that of the drug substance described in the NDA if a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to dissolution, solubility, and bioavailability.

The proposed rule would make the patent listing standards generally consistent with the ANDA approval standards. For ANDA approval purposes, the active ingredient in a generic drug product can be the ''same'' as that in the reference listed drug notwithstanding differences in the physical forms of their active ingredient if the drug product performs the same. Thus, we stated that it would be consistent to interpret ''drug substance'' for patent submission and listing purposes as including certain drug substances having different physical forms if they would be considered the same active ingredient for ANDA approval purposes (*id.*).

We invited comment on whether we should revise the codified language to require an NDA holder to submit additional information regarding the basis for its assertion that the drug substances are the ''same'' active ingredient. We also invited comment on the potential impact of the change (allowing the submission of patents claiming different polymorphs) on the submission of ANDA and 505(b)(2) applications.

(Comment 1) Several comments disagreed with our proposal to allow listing of patents claiming different polymorphs of the active ingredient in the listed drug. Some comments stated that section 505(b)(1) of the act requires the patent to claim the drug substance that is the subject of the NDA. Several comments asserted that a patent claiming a polymorph that was not the subject of an NDA did not satisfy section 505(b)(1) of the act. Other comments argued that ''sameness'' for ANDA approval purposes differed from ''sameness'' in patent law, so we did not have to develop an identical interpretation of the two concepts. Several comments maintained that no such patents could exist if the active ingredients were truly the ''same'' because a subsequent patent for the ''same'' active ingredient should not have been issued. Some comments agreed that patents claiming different polymorphs of the same active ingredient should be listed, but only with submission of additional information such as clinical trial data required for FDA approval or proof that ''sameness'' is beneficial. A few comments maintained that the proposal did not change our pre-existing position because we have permitted NDA holders and applicants to submit patents claiming different polymorphs of the active ingredient. In response to our request for comment on the impact on ANDA and 505(b)(2) applications, one comment expressed the belief that listing patents claiming different polymorphs of the active ingredient would reduce the ability of generic manufacturers to ''design around'' the existing patents, an option which was contemplated by the Hatch-Waxman Amendments.

(Response) We decline to modify our position taken in the proposed rule which would require patents to be submitted for listing that claim different polymorphs of the active ingredient described in the NDA. If the NDA applicant or holder is able to establish that a polymorph claimed in a patent is the ''same'' active ingredient (i.e., that a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to such characteristics as dissolution, solubility, and bioavailability), the NDA applicant or holder must submit the patent to us for listing. We acknowledge that there may be some legitimate confusion regarding our prior position concerning submission of such patents for listing, which resulted in the listing of some polymorph patents in the Orange Book. The uncertainty over our policy resulted from certain court decisions, our response to those court decisions, and other public statements. The FTC Citizen Petition highlighted the need for clarification and is one reason we decided to implement this final rule and clarify our position. For the reasons explained in the preamble to the proposed rule (see 67 FR 65448 at 65452 to 65453), it is appropriate to have a consistent interpretation of the ''sameness'' principle in the patent listing and ANDA approval contexts. Accordingly, we will not treat polymorphs differently for patent submission and listings and ANDA approval. The argument that certain polymorph patents should never have been issued is not a matter for us to address. The Patent and Trademark Office (PTO) is responsible for reviewing and issuing patents. We will not question whether the PTO should have issued a particular patent, nor will we conduct a ''patent law'' or other analysis to determine ''sameness.''

We agree with the comments that suggested we needed to take additional steps to help ensure that the submitted patents claim the ''same'' active ingredient as that described in the NDA. A polymorph patent must claim the drug substance (active ingredient) to meet the statutory requirements for submission. We have modified the declaration requirement and created forms to help ensure that the NDA applicant or holder or patent owner confirms that the patent does claim the ''same'' active ingredient. The final rule and the declaration forms require that the NDA applicant or holder or patent owner certify that test data exist demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. If a patent claims more than one polymorph, each polymorph for which the required test data are available must be identified by claim or description in the declaration forms.

The final rule does not require these tests to be submitted to FDA at the time of patent submission, nor does it require the NDA applicant or holder to conduct the tests itself. The testing requirements, however, will ensure that only relevant polymorphs are submitted for listing.

Whether two different polymorphs are the ''same'' active ingredient for purposes of drug approval is a scientific determination based upon the specific characteristics of the forms of the drug substance involved. Only with testing can the scientific determination be made that the drug product containing the polymorph will perform the same as the drug product described in the NDA. The test data that the NDA applicant or holder or patent owner must certify exist at the time of patent submission are similar to the type of information required under §§ 314.50 and 314.94. The following explains more fully the required tests or data that would support the statement in the declaration forms:

- A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;
- The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;
- Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;
- A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and
- Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

This test data requirement corresponds to the test data required of ANDA applicants to demonstrate the drug product containing the polymorph described in the ANDA will perform the same as the drug product described in the NDA. In addition to the data requirements described in our regulations cited above (§§ 314.50 and 314.94), we have published guidance documents describing the test data ANDA applicants may use to demonstrate that the drug product will perform the same as the drug product described in the NDA. (See ''Guidance for Industry: Changes to an Approved NDA or ANDA'' (November 1999) and ''Guidance for Industry: Immediate Release Solid Oral Dosage Forms CMS 5'' (November 1995); these guidances are available at www.fda.gov/opacom/morechoices/industry/guidedc.htm.)

The stringency of these requirements regarding ''sameness'' also should address the concerns that the submission of polymorph patents might lead to submission of other patents claiming components which are not, but might be, included in a drug described in an NDA. Given the narrow legal and scientific basis for submission of polymorph patents, the final rule does not open the door to submission of any patents claiming formulations or inactive ingredients not contained in the drug product described in the NDA.

We believe that these changes will help deter submission of inappropriate polymorph patents. The assumption that a product containing a polymorph will perform the same as the product containing a different polymorph and described in the NDA will have to be substantiated.

b. *Product-by-Process Patents—Should These Patents Be Listed?* Proposed § 314.53(b) would allow an NDA applicant or holder or patent owner to submit information on product-by-process patents. The act requires that NDA holders submit patents that claim the drug product. However, NDA applicants or holders must not submit patents that claim a process for making that product.

We explained that a product-by-process patent claims a product by describing or listing process steps to wholly or partially define the claimed product. In a product-by-process patent, the patented, novel invention is the product and not the process that is used to make the product. We recognized that the distinction between a product-by-process patent and a process patent might not be readily apparent to persons who are unfamiliar with patent law. We sought comment on ways to ensure that only appropriate product-by-process patents are listed in the Orange Book.

(Comment 2) Several comments argued that product-by-process patents must not be listed. Some comments stated that product-by-process patents ''closely resemble'' process patents and that the act does not allow listing of process patents. One comment asserted that listing product-by-process patents would have a ''profound negative effect'' on generic drug approvals because NDA applicants and holders or patent owners would attempt to list any product-by-process patent, whether or not the process defined in the patent was actually used to manufacture the drug product approved in the NDA.

Similarly, other comments sought to limit the type of product-by-process patents that could be listed. Several comments would revise the rule to require the product-by-process patent to claim a ''novel'' product, so that if the drug product described by the product-by-process patent was a ''known'' drug product or the product already had been listed in the Orange Book, we would not list the product-by-process patent. In other words, the comments sought to ensure that the product-by-process patent covered a product that was ''new and patentably distinct'' from previously-approved drug products. One comment suggested adding a new paragraph to the patent declaration to read as follows:

F. For each drug substance or drug product claim that was (1) identified as listable in subparts B and C and (2) is drafted in product-by-process format, please provide the following information:

1. Is the product of the recited process novel? [If the answer to question F.1 is ''no,'' stop. The patent cannot be listed. If yes, please identify the claim(s) by number.]

Another comment thought that few drugs would be the subject of a product-by-process patent. The comment recommended that we investigate any product-by-process patents that were listed in the Orange Book to see if these related to the NDA drug product. Yet another comment would amend the patent declaration to identify the product-by-process claims in the patent, the effective filing date of the patent application, whether the product has been previously sold, and, if the product had been previously sold, whether such sales occurred more than 1 year before the effective filing date of the patent application. The comment explained that if the drug's active ingredient has been previously sold for more than 1 year before the effective filing date of the product-by-process patent

application, the patent would be ineligible for listing because the patent would violate a specific provision in patent law.

In contrast, three comments supported listing product-by-process patents. These comments agreed that product-by-process patents are a form of a product patent. Two comments stated that we did not need to revise the rule to distinguish between product-by-process patents (which must be listed) and process patents (which must not be listed). The comment suggested revising § 314.53(b) to replace its mention of product-by-process patents with ''patents that claim the drug substance or drug product at least in part in terms of its method of manufacture (product-by-process patents).''

(Response) We agree that, to be submitted for listing, the product-by-process patent must claim the drug product that is the subject of the NDA. We explained in the proposed rule why a product-by-process patent is a type of product patent (see 67 FR 65448 at 65452). We also agree that the declaration should be clear enough to ensure that the patents that are submitted for listing are product-by-process patents and not process patents. In the response to comment 12 in section II.A of this document we detail the changes we have made to the declaration (including declaration forms) to help ensure that the patents submitted for listing are patents that claim the drug product that is the subject of the NDA and do not claim the process that is used to manufacture the drug product.

The declaration forms include a question which requires the NDA applicant or holder or patent owner to certify whether the patent being submitted is a product-by-process patent in which the product claimed is novel. Although we do not adopt the wording suggested by several comments, we agree that a requirement to identify the product as novel will help ensure that the patent is a product-by-process patent. We acknowledge that when the PTO issues a patent, the PTO necessarily determines that some aspect of the patent claims is ''novel.'' We want to make sure that the NDA applicant or holder or patent owner is identifying the product claim as the novel aspect. This clarification should eliminate the submission of patents that may be mistakenly identified as product-by-process patents but, in reality, are process patents which cannot be submitted for listing.

We expect that product-by-process patents will not be submitted often. Drug products approved under section 505 of the act typically are capable of being described by their chemical formula. Most such drug products approved are not of the type that can be described only in terms of the process used to produce the product. We decline to add any additional questions to the declaration relating to the patented product's length of time in the commercial market or other related questions, as we believe that the declaration questions we have added will accomplish the clarification necessary to prevent the submission of process patents.

c. *Patents Claiming Packaging—Do We Consider Containers and Delivery Systems to be ''Packaging*?'' Proposed § 314.53(b) would not have allowed an applicant to list a patent that claimed packaging.

(Comment 3) Most comments agreed that patents claiming packaging should not be submitted for listing. However, some comments stated that patents claiming devices or containers that are ''integral'' to the drug product or require prior FDA approval should be submitted and listed. These comments distinguished between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug.

(Response) We agree that patents claiming a package or container must not be submitted. Such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission. However, we have clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing.

Section 314.3 defines a ''drug product'' as ''* * * a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.'' The appendix in the Orange Book lists current dosage forms for approved drug products. The list includes metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems. The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not ''dosage forms.'' The revised declaration requirements, described in the response to comment 12 in section II.A of this document, detail the information required for submission.

d. *Patents Claiming Metabolites—Are Any Patents Claiming Metabolites Eligible for Submission and Listing*? The proposed rule would prohibit submission and listing of a patent claiming a metabolite of the approved drug. A metabolite is the chemical compound that results after the active ingredient of the drug has broken down inside the body. We explained that a patent claiming a metabolite does not claim the approved drug, as required by the act, because the metabolite exists only after the approved drug has been broken down inside the body (see 67 FR at 65451).

(Comment 4) Most comments agreed with our exclusion of patents claiming a metabolite. One comment, however, asked whether we would list ''a patent that claims a method of using an approved drug to administer a metabolite.'' The comment distinguished a method-of-use patent from a patent that claimed the metabolite.

(Response) The final rule prohibits submission of patents claiming metabolites when the metabolite is not the active ingredient described in the NDA. The submission of a metabolite patent does not meet the legal requirements for patent submissions as discussed in the proposed rule (see 67 FR 65448 at 65451). By contrast, if a patent submitted for listing claimed an approved method of using an approved drug to administer a metabolite, the submission of the patent would be permissible as long as all the conditions for submitting ''method-of-use'' patents are met. We describe the requirements for submission of method-of-use patents in the response to comment 7 in section II.A of this document. Briefly, if a method of use is described in the labeling for the drug product, and there is a patent claiming that method of use, the patent must be submitted for listing in the Orange Book, the method-of-use claim must be identified in the declaration forms, and the labeling language related to the method-of-use claim must be provided in the declaration forms.

e. *Patents Claiming Intermediates—Must We Allow Them to Be Submitted*? The proposed rule would not allow the submission of patents that claimed an intermediate. We explained that intermediates are materials that are produced during preparation of the active ingredient and are not present in the finished drug product. We consider intermediates to be ''in-process materials'' rather than drug substances or components in the finished drug product (see 67 FR 65448 at 65451 to 65452).

(Comment 5 and Response) The comments that addressed this issue agreed with the proposal. Consequently,

the final rule does not allow submission of patents that claim intermediates for the reasons explained in the proposal.

f. *''Double'' Patents—What Are They, and Must We Allow Them to Be Submitted*? The proposal did not discuss ''double'' patents.

(Comment 6) One comment suggested that we prohibit the listing of patents that contain a terminal disclaimer over a patent that had already been listed. The comment explained that patent law generally prevents an inventor from double patenting—that is, extending the term of the patent ''by the subsequent patenting of variations that are not patentably distinct from the first-patented invention.'' The comment stated that this ''double patenting'' can be cured if the patent holder files a ''terminal disclaimer'' which ''acts to disclaim the term of the later patent that extends beyond the term of the original patent, so that both patents expire on the same day.'' The comment expressed concern that NDA holders could list a later patent and have an opportunity to obtain a 30-month stay even if the later listed patent had a terminal disclaimer. In other words, the terminal disclaimer would prevent the inventor from enjoying a longer term of patent protection, but it would not prevent the imposition of another 30-month stay if the NDA holder or patent owner sued to enforce the later patent. The comment noted that, for the drugs PAXIL and FOSAMAX, the NDA holder had submitted earlier patents and a later-issued patent that had a terminal disclaimer. The patents were listed in the Orange Book, paragraph IV certifications were required for both patents and the NDA holder sued ANDA applicants on both patents, triggering 30-month stays.

(Response) We acknowledge that the ''double patenting'' described by the comment may, indeed, provide an NDA holder an opportunity to obtain an additional 30-month stay under the prior interpretation of the act. Under the final rule, there is no opportunity for multiple 30-month stays if patents with terminal disclaimers are submitted for listing. If such a patent is submitted after an ANDA applicant has filed a paragraph IV certification to a previously filed patent, and one full opportunity was provided for the 30-month stay, no notice need be given for a subsequent paragraph IV certification and no additional 30-month stay for that ANDA applicant can result under the final rule.

The act expressly contemplates listing of patents after NDA approval. It does not prevent an NDA holder or patent owner from submitting a patent with a terminal disclaimer. As long as the patent meets the statutory requirements, the patent must be submitted, even if it contains a terminal disclaimer. Again, we note that the PTO is responsible for the issuance of such patents. We defer to the PTO on matters of patent issuance.

g. *Method-of-Use Patents—Must the ''Use'' Be Approved in the Approved Drug Product*? The preamble to the proposed rule mentioned that patents claiming a method of use would be able to be submitted, but did not address such patents except to confirm our position that patents may not be submitted for listing if they claim methods of use that are not approved for the listed drug or are not the subject of a pending application.

(Comment 7) Comments disagreed as to whether the method-of-use claim in a patent submitted for listing must be a use approved in the NDA. Several comments urged us to list only those patents claiming methods of use approved in the NDA or that required clinical trials. One comment argued that listing only patents for approved uses was the only way to stop NDA holders from claiming broad uses or indications not in the approved labeling. In contrast, other comments argued that the act did not prevent NDA applicants or holders or patent owners from submitting patents for listing that claimed uses not approved by FDA. Some comments stated that patent infringement is not limited to approved uses. Other comments stated that section 505(b)(1) of the act contemplates the listing of patents claiming unapproved uses if a claim of patent infringement could reasonably be asserted, citing *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002) (*Purepac*).

(Response) If an NDA applicant or holder or patent owner intends to submit information on a patent that claims a method of use, the patent must claim a use that is described in the NDA. If we have already approved the NDA, the patent must claim a method of use that is in the labeling of the approved NDA. This has been our position since before we issued the final patent information rule in 1994 (see 59 FR 50338, 50363–50364 (Oct. 3, 1994)). The pre-existing requirement can be found at § 314.53(b) and (c)(2).

Sections 505(b) and (c) of the act support our position that only patents claiming approved methods of use be submitted for listing. Section 505(b)(1) of the act provides that the NDA applicant ''shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug * * * .'' The corresponding language in section 505(c)(2) of the act is nearly identical. Only method-of-use patents ''which claim the drug for which the applicant submitted the application'' must be listed. ''Drug'' is an ambiguous term, one which, for many years, we have consistently interpreted in the Hatch-Waxman Amendments to refer to the drug product. One court has said that:

> The meaning of the word ''drug'' in 21 U.S.C.§ 355(b)(1) cannot be determined apart from its context. Neither the FDA nor this court disputes that the definition of drug in § 321(g) covers both drug products and active ingredients. The relevant statutory section in this case, however, modifies the word ''drug'' by attaching the phrase ''for which the applicant submitted the application.'' In that context the FDA's interpretation of drug as meaning drug product is consistent with and indeed required by the statute.

(See *Pfizer, Inc.* v. *FDA*, 753 F. Supp. 171, 176 (D. Md. 1990).) All of the benefits afforded NDA holders under the Hatch-Waxman Amendments, such as the 30-month stay, derive from obtaining our approval of a particular drug product. Accordingly, only method-of-use patents that claim a use of the drug product in the pending or approved application must be submitted. Method-of-use patents for uses that the NDA holder ''has not chosen to make available to the public'' (*id.* at 177) must not be submitted for listing.

This construction of the statute is also supported by the more recent case law. Since we issued the proposed rule, there have been several judicial opinions discussing method-of-use patents. In *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002), and in the related case *TorPharm, Inc.* v. *Thompson*, Civ. No. 03–0254 (D.D.C. April 25, 2003) (appeal pending for both *Purepac* and *TorPharm*), the district court held that, where a patent did not claim a use approved in the NDA, an ANDA applicant could not be required to certify to that patent, and the agency could properly find that no ANDA applicant was entitled to 180-day exclusivity on that patent. In *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), the Federal Circuit held that an ANDA applicant does not need to certify to a patent claiming a use not covered by the applicable NDA, and there is no cause of action against an ANDA applicant for patent infringement under 35 U.S.C. 271(e)(2)(A) for patents that claim an unapproved use. In *Allergan, Inc.* v. *Alcon Labs., Inc.*, 324 F.3d 1322 (Fed.

Cir. 2003), the Federal Circuit issued a per curium opinion that held that a method-of-use patent holder does not have an infringement action against an ANDA applicant when the use claimed in the patent is not FDA approved and the ANDA applicant is not seeking approval of that use. These decisions are consistent with our position that sponsors must not submit method-of-use patents that do not claim an approved use for listing in the Orange Book. They also highlight the need for an improved declaration that will clarify the claimed scope of the method-of-use patents being submitted.

We have modified the required declaration relating to method-of-use patents submitted. Although we agree, as discussed in the response to comment 11 of section II.A of this document, that each individual claim of a patent does not need to be listed on the declaration forms for drug substance and drug product patents, we do require identification of individual claims for method-of-use patents. The declarant must describe each individual method of use for which a patent is submitted for listing, and identify the corresponding language found in the labeling of the approved NDA that corresponds to that method of use. This information will expedite our review of ANDA and 505(b)(2) applications that do not seek approval for all the approved uses. In determining whether an ANDA applicant can ''carve out'' the method of use, rather than certify to the listed patent, we will rely on the description of the approved use provided by the NDA holder or patent owner in the patent declaration and listed in the Orange Book.

The need for accurate and detailed information related to the approved methods of use claimed in the patent being submitted for listing is underscored by the decision in *Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002). In that case, the NDA holder submitted information on a patent claiming what was later determined to be an unapproved use of the approved drug product. This submission was accompanied by the required signed declaration from the NDA holder that the patent covered the method of use for the approved product. Accordingly, we listed the patent and the use code information submitted with the patent. Years later, well after litigation over this patent was underway, the NDA holder clarified to FDA that the patent did not, in fact, claim the use for which the NDA was approved.

This submission of inappropriate patent information led to confusion and then to litigation over an ANDA applicant's obligation to submit either a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the act or a ''section viii'' statement under section 505(j)(2)(A)(viii) of the act. The section viii statement, which is also applicable to 505(b)(2) applications, permits the ANDA or 505(b)(2) applicant to avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent. A section viii statement does not carry the requirement for notice to the NDA holder and patent owner, and the related opportunity for a 30-month stay.

We have implemented the section viii provisions of the act by deferring to the NDA holder's or patent owner's assertion that the method-of-use patent claims an approved use of the drug product. When the NDA holder or patent owner submits a method-of-use patent for an approved NDA, we rely upon the requirements in the regulations and the required declaration as the evidence that the patent claims an approved use. Therefore, when an ANDA applicant has sought to duplicate the labeling for which the innovator has submitted the patent, and not to specifically omit, or ''carve out'' labeling, we require the ANDA applicant to submit a certification to that patent. A section viii statement would not be appropriate because the ANDA applicant is seeking approval for exactly the same labeling as that in the NDA for which the patent was submitted.

Our position has been that, for an ANDA applicant to file a section viii statement, it must ''carve out'' from the proposed ANDA labeling, the labeling protected by the listed patent. Unless the ANDA applicant can show that it is carving out certain method-of-use labeling, a section viii statement is not a correct submission for the listed patent. In *Purepac*, the court rejected our reliance on the regulations and the general declaration as a reasonable basis for this approach to implementation. The court specifically pointed to the patent submissions in the case, and noted that the NDA holder had not complied with the requirement that NDA holders submit only those patents claiming an approved use for the drug. Although the court noted that the facts in *Purepac* were unique (the NDA holder later admitted that it made its submission ''without regard'' to FDA's regulations), there may be other cases in which NDA holders have submitted patents claiming unapproved uses of approved drug products.

Following the *Purepac* decision, we have two options for implementing the section viii statement provisions under sections 505(b)(2)(B) and 505(j)(2)(A)(viii) of the act that intersect with the patent submission considerations described in the proposed rule. One approach would be to permit each ANDA and 505(b)(2) applicant to make its own independent decision on whether a listed method-of-use patent claims the use for which the ANDA applicant seeks approval, and then to submit a paragraph IV certification or section viii statement as the applicant sees fit. The second approach would be to require the NDA applicant or holder to identify specifically the approved uses claimed by the method-of-use patent, with reference to the approved labeling, and declare under penalty of perjury that the patent claims an approved use. This would permit ANDA and 505(b)(2) applicants, and us, to assess whether the ANDA or 505(b)(2) applicant is seeking approval for a use the sponsor states is claimed in the listed patent, and thus determine whether the applicant must submit a patent certification or may submit a section viii statement under section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the act.

In the absence of explicit statutory language, we believe an approach that requires the NDA applicant or holder or patent owner to identify the approved methods of use protected by the patent is most consistent with the general balance adopted in Hatch-Waxman. This approach permits the NDA applicant or holder to determine which patents claim its approved drug product and then, when appropriate, to resolve disputes over infringement of those patents through patent litigation. If ANDA and 505(b)(2) applicants could always avoid the possibility of a 30-month stay by asserting in a section viii statement that certain labeling for which the applicant is seeking approval is not protected by a listed method-of-use patent—despite the NDA holder's assertion to the contrary—there would be little reason for any applicant to submit a paragraph IV certification for a method-of-use patent. This approach would essentially eliminate the certification, notice, and litigation process as to any listed method-of-use patent, producing an outcome that is inconsistent with the act.

To effectively implement the certification and section viii statement provisions set out in the statute, we must have adequate information concerning method-of-use patents. Since 1994, we have requested, but not required, that NDA applicants submit to FDA information on the approved use claimed by the patent. Since the

Purepac case and other instances have raised questions about what aspects of the approved drug are claimed by a listed use patent, we believe that it is necessary that an NDA holder submit more specific information on the approved methods of use protected by a submitted patent. Only with this information can we determine what submission is required of the ANDA and 505(b)(2) applicants referencing the approved drug.

We further note that we list methods of use for approved products in the Orange Book in the section on use codes. Due to the limitations of our database system and software constraints, we are limited to using 240 total characters for the use code description in the Orange Book. Traditionally, we have created the use code description for the Orange Book from the information submitted by the NDA applicant or holder. After considering the comments, and in light of the previously described litigation, we have determined that it is more efficient and accurate to ask the NDA holder to give us the exact use code description to be published in the Orange Book. Use codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. They are not meant to substitute for the applicant's review of the patent and the approved labeling. We understand that in some cases 240 characters may not fully describe the use as claimed in the patent. The declaration, which includes the complete description of the method-of-use claim and the corresponding language in the labeling of the approved drug, will be publicly available after NDA approval.

h. *Miscellaneous Patent Listing Comments*. i. *Should We Create an Administrative Process to Challenge Patent Listings or to De-List Patents or to Review the Listability of Patents*? The proposed rule did not propose an administrative process for challenging patent listings or for seeking removal of a patent from the Orange Book, nor did we propose a new process to internally review the patents for listability.

(Comment 8) Several comments stated that parties, such as generic drug companies and even third parties, need a method for challenging patent listings or for de-listing patents in the Orange Book. Some comments explained that the lack of an administrative procedure for challenging patent listings either encouraged NDA applicants to submit inappropriate patent information, or did not deter the practice, to delay generic competition. A number of comments maintained that FDA has more than a ministerial role and should review patents to determine if they meet the requirements for listing. Several comments contend that we have the authority to determine the attributes of the approved drug and thus to determine the appropriate patent listings. Various administrative mechanisms were suggested through which FDA could conduct a review of patents. These suggestions ranged from hiring patent lawyers to review submitted patents to development of a full administrative hearing process.

One comment stated that patent owners need an administrative process to enforce the listing of their patents because an NDA holder might ''fail'' to list eligible patents.

(Response) A fundamental assumption of the Hatch-Waxman Amendments is that the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents. The courts have the experience, expertise, and authority to address complex and important issues of patent law. This final rule supports that assumption in two ways. First, the final rule clarifies what patents must and must not be submitted for listing. This will make it easier for NDA applicants and holders and patent owners to avoid inadvertently submitting patents that do not meet the statutory and regulatory requirements. The clarification will reduce the pressure on us to intercede in patent listing disputes and will allow the courts and parties to focus on the ultimate issue of patent invalidity or non-infringement. Second, the final rule requires NDA applicants or holders or patent owners to submit detailed information and to certify to its correctness. This should further ensure that only patents meeting the statutory requirements will be submitted for listing.

We decline to create an additional administrative process for challenging patent listings beyond that already established in § 314.53(f). We also decline to create a new process for de-listing patents or for internal FDA review of patents beyond the limited review of the patent declaration described in this final rule. Section 505(b)(1) of the act directs NDA applicants to submit certain patent information. It requires that ''[u]pon approval of the application, the Secretary shall publish'' the patent information (emphasis added). In section 505(j)(7)(A)(ii) and (iii) the statute mandates that we publish revisions to this information every 30 days. These short time frames do not contemplate a substantive agency review of the scope of the patent and its application to the approved drug product. Indeed, the requirement of prompt publication (''upon submission''), combined with the 30-day timeframe for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.

In addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority. Although we will continue to relay questions about the accuracy of a patent submission to the NDA holder (see § 314.53(f)), our patent listing role remains ministerial. Courts have upheld our determination that our role with respect to patent listing is ministerial. (See *aai Pharma* v. *Thompson*, 296 F.3d 227, 242–43 (4th Cir. 2002), cert. denied, 123 S. Ct. 1582 (2003); *American Biosci., Inc.* v. *Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001); *In re Buspirone Patent Litigation*, 185 F. Supp. 2d 363, 371 (S.D.N.Y. 2002); *Watson Pharm., Inc.* v. *Henney*, 194 F. Supp. 2d 442, 445–446 (D. Md. 2001); *Mylan Pharm., Inc.* v. *Thompson*, 139 F. Supp. 2d 1, 10–11 (D.D.C.), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).) We recognize that one court has held that parties have no private right of action to seek de-listing of patents (see *Mylan Pharmaceuticals, Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001)). Nevertheless, it would be inappropriate and impractical for us to create regulatory mechanisms for reviewing patent listings or permitting third parties to submit patents for listing. We lack both the resources and the expertise to resolve such matters.

Furthermore, even if we were to establish an administrative process for patent review, our decisions on these patent listing matters would inevitably lead to disputes and increased litigation against us. This litigation could question whether such an administrative process was within our legal authority. Even if the courts were to decide that we may review submitted patents, there would be repeated litigation over individual patent listing decisions. Given the uncertainty of the listing status of the challenged patent during the litigation, there is no assurance that, if we reviewed submitted patents, ANDAs or 505(b)(2) applications would be approved sooner and generic drugs would enter the market any more rapidly.